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UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF CALIFORNIA

CADENCE PHARMACEUTICALS,  
INC. and SCR PHARMATOP,

Plaintiffs,

v.

FRESENIUS KABI USA, LLC,

Defendant.

AND RELATED COUNTERCLAIMS

**CASE NO. 13-CV-00139 DMS (MDD)**

**EXHIBIT B TO PLAINTIFFS'  
SUPPLEMENTAL MEMORANDUM  
IN OPPOSITION TO FRESENIUS'S  
EX PARTE MOTION FOR  
SANCTIONS**

Magistrate Judge: Mitchell D. Dembin

# **EXHIBIT B**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Application Number : 90/012,606 Confirmation No.: 2222  
Patent Number : 6,028,222  
Filed : August 5, 1997  
Title : Stable Liquid Paracetamol Compositions, and Methods for Preparing  
: Same  
TC/Art Unit : 3991  
Examiner: : Gary L. KUNZ  
  
Attorney Docket No. : 58766.001010  
Customer No. : **21967**

**MAIL STOP *EX PARTE* REEXAM**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**RESPONSE TO FIRST OFFICE ACTION**

Sir:

The Patent Owner, SCR Pharmatop (“Pharmatop” or “Patent Owner”), is the assignee of all right, title and interest in and to U.S. Patent No. 6,028,222 (“the ‘222 patent”), which is the subject of the pending reexamination. Pharmatop respectfully submits this Response to the first Office Action mailed August 13, 2013. The August 13, 2013 Office Action set forth a two-month response period which expired October 13, 2013. The United States Patent & Trademark Office (“Patent Office”) granted Patent Owner a two-week extension of time on September 18, 2013. The Patent Office granted Patent Owner a second two-week extension of time on October 24, 2013. The deadline for response in view of the four-weeks of extension is November 10, 2013. Because this day falls on a Sunday, and the following Monday is a Federal holiday (Veteran’s Day), this response is being filed on Tuesday, November 12, 2013. The USPTO is authorized to charge any fees it deems necessary for the filing of this response to Deposit Account No. 50-0206.

Included with this Response, please find the following:

Pages 3-7: Claim Amendments;

APPLICATION NO. 90/010,464  
ATTY DOCKET NO. 58766.001010

Pages 8-24: Remarks;

Exhibit A – OFIRMEV® Prescribing Information

Declaration of William Craig, Ph.D. (“Craig”);

Declaration of François Dietlin, Ph.D. (“Dietlin”);

Declaration of Edmund J. Elder, Ph.D, R.Ph. (“Elder”)

Declaration of Asokumar Buvanendran, M.D. (“Buvanendran”)

Declaration of Gregory K. Bell, Ph.D. (“Bell”)

**Please amend the claims as follows:**

1. (Original) A stable, liquid formulation consisting essentially of acetaminophen dispersed in an aqueous medium containing a buffering agent and at least one member of the group consisting of a free radical scavenger and a radical antagonist.
2. (Original) The formulation of claim 1 wherein the aqueous medium has been deoxygenated by bubbling a water-insoluble inert gas.
3. (Original) The formulation of claim 1 wherein the aqueous medium is buffered at a pH of 4 to 8.
4. (Original) The formulation of claim 3 wherein the aqueous medium is buffered at a pH of 5.5 to 6.
5. (Once Amended) The formulation of claim 1 containing a free radical antagonist selected from the group consisting of ascorbic acid, ascorbic acid derivatives, organic compounds having at least one thiol, and [a] alkyl polyhydroxylated and cycloalkyl polyhydroxylated compounds.
6. (Original) The formulation of claim 5 wherein the ascorbic acid derivatives are selected from the group consisting of D-ascorbic acid, L-ascorbic acid, alkali metal ascorbates, alkaline earth metal ascorbates and water-soluble ascorbic acid esters.
7. (Original) The formulation of claim 5 wherein the organic compound having at least one thiol is aliphatic or cycloaliphatic.
8. (Once Amended) The formulation of claim 1 containing a free radical scavenger containing at least one thiol [is] selected from the group consisting of [thiolyglycolic] thioglycolic acid, [thiolacetic] thioacetic acid, dithiothreitol, reduced [glutathion] glutathione, thiourea,  $\alpha$ -thioglycerol, cysteine, acetylcysteine and mercaptoethane sulfonic acid.

9. (Once Amended) The formulation of claim 1 wherein the free radical scavenger is an aliphatic polyhydroxy [alkanol]alcohol of 2 to 10 carbon atoms.

10. (Once Amended) The formulation of claim 9 wherein the polyhydroxy [alkanol]alcohol is a cyclic glucitol or a straight chain glucitol of 6 to 10 carbon atoms.

11. (Once Amended) The formulation of claim 9 wherein the polyhydroxy [alkanol]alcohol is glycerol or propyleneglycol.

12. (Original) The formulation of claim 10 wherein the cyclic glucitol is selected from the group consisting of mannitol, sorbitol, inositol, glucose and levulose.

13. (Original) The formulation of claim 1 also containing at least one complexing agent.

Claims 14-15 are cancelled.

16. (Once Amended) The formulation of claim [14] 1 wherein the acetaminophen is diluted to a concentration of 2 to 50 mg/ml.

17. (Original) The formulation of claim 1 also containing an isotonizing agent in an amount to obtain isotonicity.

18. (Original) The formulation of claim 1 sterilized by heat treatment.

19. (Original) The formulation of claim 1 further containing an effective amount of an analgetic agent.

20. (Original) The formulation of claim 19 the analgetic agent is a morphine analgetic selected from the group consisting of natural morphines, semi-synthetic morphines, synthetic morphines, phenylpiperidines, nipecotic acid compounds, phenylcyclohexanol compounds and phenylazepine compounds.

21. (Original) The formulation of claim 20 having a concentration of acetaminophen is 0.05 to 5% by weight when morphine is present.

22. (Original) The formulation of claim 20 having an acetaminophen concentration of 0.2 to 2.5% by weight when codeine is present.

23. (Original) The formulation of claim 1 further containing an anti-inflammatory agent of the phenylacetic acid type.

24. (Original) The formulation of claim 23 wherein the anti-inflammatory agent is ketoprofen.

25. (Original) The formulation of claim 1 further containing an antiemetic agent.

26. (Original) The formulation of claim 1 further containing an antipileptic agent.

27. (Original) The formulation of claim 1 further containing a corticosteroid.

28. (Original) The formulation of claim 1 further containing a tricyclic antidepressant.

Add new claims 29-43.

29. The liquid formulation of claim 1, wherein the acetaminophen has a concentration of 5 to 20 mg/mL, pH is 5.5 to 6, and at least one member of the group consisting of a free radical scavenger and a radical antagonist is selected from the group consisting of ascorbic acid derivatives, organic compounds having at least one thiol and an alkyl polyhydroxylated and cycloalkyl polyhydroxylated compounds.

30. The liquid formulation of claim 1, wherein the formulation is deoxygenated, acetaminophen has a concentration of 5 to 20 mg/mL, the pH is 5.5 to 6, and at least one member of the group consisting of a free radical scavenger and a radical antagonist is selected from the group consisting of ascorbic acid derivatives, organic compounds having at least one thiol and an alkyl polyhydroxylated and cycloalkyl polyhydroxylated compounds.

31. The liquid formulation of claim 1, wherein the formulation has a pH of 4 to 6.

32. The liquid formulation of claim 1, wherein the formulation is injectable.

33. The liquid formulation of claim 1, wherein the formulation is intravenously infusable.

34. The liquid formulation of claim 1 wherein the aqueous medium is a mixture of water and a polyhydric compound or a water-soluble alkanol, the polyhydric compound or water-soluble alkanol is in a concentration of less than 10%, the acetaminophen concentration is 5 to 20 mg/mL and pH is 4 to 6.

35. The liquid formulation of claim 34 wherein the acetaminophen concentration is 5 to 20 mg/mL.

36. The liquid formulation of claim 34 wherein the pH is 5.5 to 6.

37. The liquid formulation of claim 5 wherein the acetaminophen concentration is 2 to 50 mg/mL and pH is 4 to 6.

38. The liquid formulation of claim 37 wherein the acetaminophen concentration is 5 to 20 mg/mL.

39. The liquid formulation of claim 37 wherein the pH is 5.5 to 6.

40. A stable, isotonic, liquid formulation of acetaminophen consisting essentially of acetaminophen dispersed in a deoxygenated aqueous medium containing a buffering agent and at least one member of the group consisting of a free radical scavenger and a radical antagonist, wherein the at least one member of the group consisting of a free radical scavenger and a radical antagonist is selected from the group consisting of ascorbic acid derivatives, organic compounds having at least one thiol, and alkyl polyhydroxylated and cycloalkyl polyhydroxylated compounds, wherein the aqueous medium is a mixture of water and a polyhydric compound or a

water-soluble alkanol, the pH is 4 to 6, and the concentration of acetaminophen is 2 to 50 mg/mL.

41. The liquid formulation of claim 40 wherein the pH is 5.5 to 6.

42. The liquid formulation of claim 40 wherein the concentration of acetaminophen is 5 to 20 mg/mL.

43. A stable, isotonic, liquid formulation of acetaminophen consisting essentially of acetaminophen dispersed in a deoxygenated aqueous medium containing a buffering agent and at least one member of the group consisting of a free radical scavenger and a radical antagonist, wherein the at least one member of the group consisting of a free radical scavenger and a radical antagonist is selected from the group consisting of mannitol and cysteine hydrochloride, wherein the aqueous medium is a mixture of water and a polyhydric compound or a water-soluble alkanol, the pH is 5.5 to 6, and the concentration of acetaminophen is 2 to 20 mg/mL.

### Remarks

Please find these Remarks addressing the Office Action mailed August 13, 2013. Claims 1-6 and 8-19 are subject to reexamination and stand rejected. Patent Owner hereby amends claims 5, 8-11, and 16 of the '222 patent, and adds new claims 29-43. Claims 14-15 are cancelled. Support for the amendments and new claims is explained below. Attached as Exhibit A, please find the FDA-approved prescribing information for OFIRMEV® (acetaminophen) injection, for which the '222 patent is listed in the Orange Book. The following declarations are also attached to these Remarks:

- Declaration of William Craig, Ph.D. ("Craig") discussing comparative testing of the commercial embodiment, OFIRMEV®, relative to the examples of three prior art references.
- Declaration of François Dietlin, Ph.D. ("Dietlin") discussing testing of various embodiments of the claimed invention for stability.
- Declaration of Edmund J. Elder, Ph.D, R.Ph. ("Elder") discussing technical issues related to the prior art relied on in the Office Action.
- Declaration of Asokumar Buvanendran, M.D. ("Buvanendran") regarding secondary factors of non-obviousness.
- Declaration of Gregory K. Bell, Ph.D. ("Bell") regarding certain economic considerations related to the commercial success argument.

In view of the following, Patent Owner respectfully requests reconsideration and confirmation of claims 1-6, 8-13, and 16-19 under reexamination.

### Introduction

The '222 patent claims the first approved and commercially marketed injectable formulation of acetaminophen (*i.e.*, paracetamol or N-acetyl-p-aminophenol) in the United States, OFIRMEV® (acetaminophen) injection. Buvanendran, ¶ 47. The European equivalent is

Perfalgan® (paracetamol) solution for infusion, launched in 2002. *Id.* According to its prescribing information:

OFIRMEV injection is a sterile, clear, colorless, non pyrogenic, isotonic formulation of acetaminophen intended for intravenous infusion. It has a pH of approximately 5.5 and an osmolality of approximately 290 mOsm/kg. Each 100 mL contains 1000 mg acetaminophen, USP, 3850 mg mannitol, USP, 25 mg cysteine hydrochloride, monohydrate, USP, 10.4 mg dibasic sodium phosphate, USP. pH is adjusted with hydrochloric acid and/or sodium hydroxide.

Exhibit A (OFIRMEV prescribing information).

The ‘222 patent addressed a long felt yet unmet need in the marketplace for a “stable, liquid formulation consisting essentially of acetaminophen dispersed in an aqueous medium” suitable for injection. The closest injectable composition on the marketplace was sold in Europe as a prodrug of acetaminophen under the trade name pro-Dafalgan®. *Id.*, ¶ 50. The instability of pro-Dafalgan in water was widely recognized—it was sold as a powder that had to be reconstituted. *Id.* Reconstitution entailed risks for the healthcare provider and precluded use of pro-Dafalgan in time sensitive, emergency circumstances. *Id.*, ¶ 50-51. Finally, pro-Dafalgan users experienced “high incidence of pain at injection site.” *Id.*, ¶ 51.

The ‘222 patent’s commercial product OFIRMEV® and its European equivalent Perfalgan® are commercially successful, and that success derives from these products being the first stable, liquid injectable form of acetaminophen. By second quarter 2012, OFIRMEV® accounted for 66 percent of U.S. sales of non-opioid analgesics suitable for IV administration. Bell, ¶ 9. Since its launch in 2002, Perfalgan (identical to OFIRMEV®) became the top grossing non-opioid analgesic suitable for IV administration in France, Germany, Spain, Italy, and the United Kingdom. *Id.*, ¶ 10. The ‘222 patent product achieved these sales even though they have a wholesale acquisition cost (WAC) that is approximately 170 times that of acetaminophen tablets and 40 times that of acetaminophen suppositories. *Id.*, ¶ 11. Finally, the commercial success of OFIRMEV is not due to marketing or the merits of acetaminophen in general. *Id.*, ¶ 12.

The '222 patent teaches that the problem with liquid injectable formulations of acetaminophen at the time of the invention was lack of stability. The key breakthrough of the '222 patent invention was the discovery by the inventors that the degradation of acetaminophen involves first an oxidative process followed by hydrolysis. Elder, ¶¶44; '222 patent, col. 10, ll. 41-43. To this end, the '222 patent requires a *stable*, liquid composition. Stability, according to the '222 patent, requires the absence of secondary peaks using an HPLC analysis. Further, the specification makes clear that stability requires, in addition to careful choice of the carrier, "careful adjustment of pH, removal of oxygen dissolved in the carrier and addition of a free radical antagonist or a free radical scavenger." '222 patent, col. 2, ll. 31-35. Each of the cited references lacks one or more of the claimed features, results in an unstable product, and fails to render the claimed invention obvious.

Injectable acetaminophen compositions prepared in accordance with the processes described in the '222 patent exhibit the unexpected stability. The grounds of rejection are based on three primary references: (1) GR870101510B ("GR '510"), (2) KR 1993-0011994 ("KR '994"), and (3) U.S. Patent No. 5,270,050 ("Coquelet"). Each of the prior art references cited lacks the claimed stability limitation as shown by the presence of secondary peaks in an HPLC analysis. Craig, ¶¶ 16, 19, 22, 25, 27, 29. The testing by Dr. Craig confirms this lack of stability. Craig, ¶¶ 37, 38, 39. The lack of stability in these products can be understood in light of the '222 patent's teaching, since the prior art references fail to follow the teachings of the '222 patent with respect to obtaining a stable, liquid acetaminophen composition.

Claims 5-12 recite specific free radical antagonists having improved characteristics that contributed to the success of OFIRMEV. None of the cited references disclosing liquid acetaminophen compositions, GR '510, KR '994, or Coquelet, utilize the specifically claimed free radical antagonists set forth in claim 5. These references included sodium metabisulfite. The Office Action proposes that it would have been obvious to replace the sodium metabisulfite of GR '510, KR '994 and/or Coquelet, with any known antioxidant. To support this assertion, the Office cites Handbook '79 which lists several known antioxidants, but fails to provide motivation for selecting any compounds set forth in claims 5-12. Patent Owner submits herewith

additional evidence of unexpected results using the free radical antagonists listed in claims 5-12. Because this showing of unexpected results is reasonably commensurate in scope with the claims, Patent Owner respectfully submits that the showing of unexpected results weighs strongly in favor of non-obviousness of claims 5-12. Further, the above noted commercial success and satisfaction of a long felt need for a liquid injectable form of acetaminophen further support the non-obviousness of these claims.

### **Claim Amendments**

Original claims 5, 8, 9-11, and 16 are amended, claims 14-15 are cancelled, and claims 29-43 are new. The amended claims show changes relative to the '222 patent as modified by the certificate of correction dated November 13, 2010. The amended and new claims do not broaden the claim scope of the '222 patent, and are supported by the original disclosure, as explained below.

Claim 5 has been amended to place commas after ascorbic acid and thiol. The commas separate the three categories of free radical antagonist and provide better grammatical flow for the claim. The term "a" has been removed before "alkyl polyhydroxylated and cycloalkyl polyhydroxylated compounds" to reflect the fact that the claim lists the three categories in the plural, which is inconsistent with the use of the indefinite article "a." These merely grammatical changes are supported by the original disclosure.

Claim 8 has been amended to delete "is" after "thiol." This change corrects a grammatical error. The claim has also been amended to correct several spelling errors including:

- Replacing "thiolyglycolic" with --thioglycolic--.
- Replacing "thiolacetic" with --thioacetic--.
- Replacing "glutathion" with --glutathione--.

Claims 9-11 have been amended to replace alkanol with alcohol. This is a typographical error in the claims. Support for this amendment is found at col. 2, ll. 54-56 of the '222 patent.

Claim 16 has been amended to correct a dependency issue in view of cancellation of claims 14-15.

New claims 29-39 depend from claim 1 and include combinations of various dependent claim limitations set forth in the original patent, along with new limitations with support found in the specification. Exemplary support for the new limitations are found as follows:

- Concentration of 5 to 20 g/mL ('222 patent, col. 3, ll. 54-56)
- Formulation is injectable ('222 patent, col. 3, ll. 45-46)
- Formulation is intravenously infusible ('222 patent, col. 3, ll. 49-51)
- Water soluble alkanol is between 5 and 10 mg/ml ('222 patent, col. 5, ll. 9-10)
- pH is 4 to 6. ('222 patent, claim 3 and examples at pH of 6)
- Deoxygenated ('222 patent, col. 2, ll. 30-35)

New claims 40-43 include new claims 41 and 44 in independent form. These claims include the limitations of independent claim 1 and add many features already present in dependent claims or discussed immediately above with respect to claims 29-39.

### **Grounds of Rejection**

The Office Action sets forth the following fourteen grounds of rejection under relying on three primary references: GR870101510B ("GR '510"), KR 1993-0011994 ("KR '994"), and U.S. Patent No. 5,270,050 ("Coquelet"):

1. Claims 1-3, 13-15, and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by GR '510.
2. Claims 4 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over GR '510.
3. Claims 5, 6, 8, 10, and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over GR '510 as applied to claims 1-3, 9, 11, 13-15, and 19, further in view of Handbook '79 and Cole.
4. Claim 17 is rejected under 35 U.S.C. § 103(a) as being unpatentable over GR '510 as applied to claims 1-3, 9, 11, 13-15, and 19, further in view of EP '043.
5. Claim 18 is rejected under 35 U.S.C. § 103(a) as being unpatentable over GR '510 as applied to claims 1-3, 9, 11, 13-15, and 19, further in view of Barton '310.

6. Claims 1, 3, 9, 11, 14, 15, 17 and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by KR '994.
7. Claims 16 and 19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over KR '994 as evidenced by Hayatsu.
8. Claims 2 and 4 are rejected under 35 U.S.C. § 103(a) as being unpatentable over KR '994 as applied to claims 1, 3, 9, 11, 14, 15, 17 and 18, further in view of Handbook '79.
9. Claims 5, 6, 8, 10, 12, and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over KR '994 as evidenced by Hayatsu and as applied to claims 1, 3, 9-11, 14, 15, 17 and 18, further in view of Handbook '79 and Cole.
10. Claims 1, 3, 13, 14, and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Coquelet.
11. Claim 2 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Coquelet as applied to claims 1, 3, 13, 14 and 16, further in view of Handbook '79.
12. Claims 5, 6, and 8-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Coquelet as applied to claims 1, 3, 13, 14 and 16, further in view of Handbook '79 and Cole.
13. Claims 9, 11 and 17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Coquelet as applied to claims 1, 3, 13, 14 and 16, further in view of EP '043.
14. Claim 18 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Coquelet as applied to claims 1, 3, 13, 14 and 16, further in view of Barton '310.

For the reasons discussed below, Patent Owner respectfully requests reconsideration and confirmation of the claims under reexamination.

#### *Anticipation*

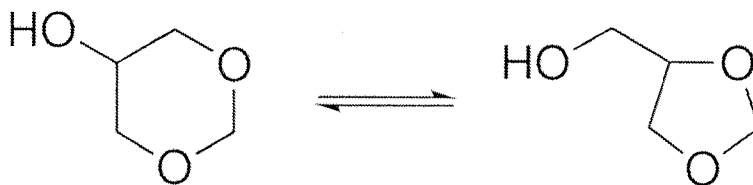
**Claims 1-3, 13-15, and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by GR '510.**

The invention of claim 1 is a *stable*, liquid formulation *consisting essentially of acetaminophen dispersed in an aqueous medium*, as follows:

A stable, liquid formulation consisting essentially of acetaminophen dispersed in an aqueous medium containing a buffering agent and at least one member of a group consisting of free radical scavenger and a radical antagonist.

First, GR '510 does not described a "stable" formulation as that claim is interpreted in light of the '222 patent specification. As acknowledged by the examiner, "stable" means "[t]he active pharmaceutical ingredient does not decompose substantially such that the formulation has a pharmaceutically acceptable shelf life." OA at 5. Testing by Dr. Craig shows that the GR '510 product exhibited a large eluting peak at 9.6 minutes, and a large number of additional peaks as a result of degradation. Craig, ¶¶ 39. These data show that the GR '510 product exhibits considerable instability at 60°C for 18 days. Craig, ¶¶39, 47. The GR '510 product will exhibit a shelf life of less than 85 days at room temperature. Craig, ¶ 52 (Table 2).The instability of GR '510 is likely due to the use of high levels of glycerol formal, which were probably considered necessary to solubilize the high acetaminophen dose described in that application. Craig, ¶39.

Second, GR '510 does not disclose an "aqueous medium" as claimed. The examiner has defined the term "aqueous medium" to mean "A solution of acetaminophen dissolved in a medium containing water or aqueous mixtures of water and a polyhydric compound and/or water soluble alcohol." Office Action at 5. The quoted portion of the patent does not refer to water soluble alcohol, and instead refers to "alca-nol." '222 patent, col. 2, ll. 22-27. But this passage of the patent was corrected to replace "alca-nol" with "alkanol." See '222 patent, certificate of correction mailed November 13, 2010. The certificate of correction changes "alca-nol" to "alkanol." Glycerol formal is not an alkanol. Glycerol formal is a mixture of cyclic ether compounds having 2 oxygen atoms in the ring structure and substituted by a single alcohol group:



Because glycerol formal makes up 49% of the solvent system in GR '510 and does not meet the definition of aqueous medium set forth in the '222 patent, GR '510 fails to anticipate claim 1. Given Dr. Craig's observation of a large number of additional peaks compared to the '222 products and other prior art not using glycerol formal, Dr. Craig has opined that the presence of large amounts of glycerol formal may be responsible for the degradation seen in GR '510. Craig, ¶ 39.

Third, GR '510 does not disclose a pharmaceutically acceptable form of acetaminophen. Glycerol formal used in GR '510 is toxic, and the maximum daily intake allowed precludes its use as a formulation for acetaminophen. Elder, ¶¶ 53.

For at least these reasons, GR '510 does not anticipate claim 1. Claims 2-3, 13, and 19 depend from and incorporate the limitations of claim 1 and are also not anticipated for the reasons above.

**Claims 1, 3, 9, 11, 14, 15, 17 and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by KR '994.**

KR '994 discloses a "method for improving the bioavailability of paracetamol and a formulation containing the paracetamol with improved bioavailability." KR '994 at 1. KR '994 focuses on increasing bioavailability by adding agents such as propylene glycol, which when not added resulted in the paracetamol being "barely dissolved." KR '994 at 5.

KR '994 does not described a "stable" formulation as that claim is interpreted in light of the '222 patent specification. The term "stable" means "[t]he active pharmaceutical ingredient does not decompose substantially such that the formulation has a pharmaceutically acceptable shelf life." OA at 5. Testing by Dr. Craig shows that the KR '994 product exhibited a large eluting peak at 14.5 minutes. Craig, ¶ 38. These data show that the KR '994 product exhibits considerable instability at 60°C at the 18 day time point. Craig, ¶¶ 38, 47, and that the KR '994 product will exhibit a shelf life of less than 85 days at room temperature. Craig, ¶ 52 (Table 2).

KR '994 purports to describe stability testing. However, the stability testing was conducted using Examples 2 and 5 of KR '994, neither of which includes a buffer or at least one

member of a group consisting of free radical scavenger and a radical antagonist. Further, the test for stability in KR '994 is whether the composition exhibited less than 1% P-aminophenol. But compositions containing just under 1% P-aminophenol would be considered unstable according to the '222 patent definition. This is because the '222 patent uses the existence of secondary peaks by HPLC as a qualification method for stability. As shown by Dr. Craig's testing, the KR '994 product exhibited secondary peaks at the 14.5 minute and 20 minute elution time of 2.41 and 1.25 percent respectively after 15 days at 60°C. Further, under the '222 patent construction of stability as requiring a pharmaceutical acceptable shelf life, the threshold level of degradation is 0.05%. Craig, ¶ 53. Thus, the KR '994 test for instability does not demonstrate whether or not the product would be stable using an HPLC analysis for stability. Dr. Craig's testing shows that, in fact, the KR '994 product is not stable under the correct definition for the '222 patent.

The lack of buffer and corresponding instability of KR '994 is apparent in the reference itself. The KR '994 discloses several injectable compositions, including Examples 1-5. These examples are not described as having a buffer. Although KR '994 makes reference to pH regulators, these components are described as alternative adjuvants in the Markush claim 3. The Markush group of claim 3 does not recite combinations of the separately listed elements. It is well understood that qualifying language such as "and mixtures thereof" is necessary for a Markush group to be understood as disclosing combinations of the listed elements. *See Abbott Laboratories v. Baxter Pharmaceutical*, 334 F. 3d 1274, 1281 (Fed. Cir. 2003) ("If a patentee desires mixtures or combinations of the members of the Markush group, the patentee would need to add qualifying language while drafting the claim. *See Meeting Held to Promote Uniform Practice In Chemical Divisions*, supra, at 852 (citing examples of qualifying language such as: "and mixtures thereof" and "at least one member of the group)"). Therefore, claim 3 does not support that KR '994 discloses a combination of a buffer and antioxidant within a single composition.

Further, the broad description of KR '994 mentions buffers such as Gifford's buffer solution, Palitzsch's buffer solution, Hind-Goyan's buffer solution and Sorenson's buffer solution. KR '994 at 3. The reference fails to describe a composition having all the components

of claim 1 as required by the claim. For its teaching of a buffer, the Office action points to the following paragraph of KR '994:

According to the present invention, all sorts of formulations can be prepared according to all the typical types of methods, by adding, to the paracetamol composition of the present invention, at least one of an excipient that is generally used in preparing injections, powders, tablets, capsules, syrups or suppositories, for example, lactose, all sorts of starches, white sugar, mannitol, sorbitol or inorganic salt (e.g., calcium phosphate, aluminum silicate, calcium sulfate and the like); a binding agent such as sucrose, glucose, starch, gelatin, carboxymethyl cellulose, methylcellulose, gum arabic, methylcellulose, hydroxypropylmethylcellulose or polyvinylpyrrolidone; lubricant such as cornstarch, talc, magnesium stearate, calcium stearate and waxes; humectants such as glycerin, sorbitol and the like; solvents, such as water; buffers such as Gifford's buffer solution, Palitzsch's buffer solution, Hind-Goyan's buffer solution and Sorensen's buffer solution; isotonicizing agents such as sodium chloride; preserving agents such as para-hydroxybenzoic acid esters; cationic detergent; all kinds of organic acids; antibiotics; pain relievers such as benzyl alcohol, chlorobutanol and all sorts of local anesthetics; and ointments or suppositories such as Vaseline, paraffin, plastibase, silicone, lard, benzoic lard, vegetable oils, waxes, emulsion substrate, water-soluble substrate, hydrogel-based compound and the like.

KR '994 at 3. The number of combinations of potential formulations based on this paragraph is very large. "Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, *arranged as in the claim*." *Lindemann Maschinenfabrik v. Am. Hoist and Derrick*, 730 F. 2d 1452 (Fed. Cir. 1984) (emphasis added). Because there is no disclosure in KR 994 of every claimed component as arranged in the claim, KR '994 does not anticipate the claim.

For at least these reasons, KR '994 does not anticipate claim 1. Claims 3, 5, 6, 9–12, 17, and 19 depend from and incorporate the limitations of claim 1 and are also not anticipated for the reasons above.

**Claims 1, 3, 13, 14, and 16 are rejected under 35 U.S.C. §102(b) as being anticipated by Coquelet.**

The Coquelet reference discloses an ophthalmic composition in Example 1. Coquelet does not described a “stable” formulation as that claim is interpreted in light of the ’222 patent specification. The term “stable” means “[t]he active pharmaceutical ingredient does not decompose substantially such that the formulation has a pharmaceutically acceptable shelf life.” OA at 5. Testing by Dr. Craig shows that the Coquelet product shows a major degradation peak at 14.7 minutes, which was identified as a dimer of acetaminophen. Craig, ¶ 37. The Coquelet product will exhibit a shelf life of less than 31 days at room temperature. Craig, ¶ 52 (Table 2).

For at least these reasons, Coquelet does not anticipate claim 1. Claims 3, 13, and 16 depend from and incorporate the limitations of claim 1 and are also not anticipated for the reasons above.

### ***Obviousness***

Several obviousness rejections has been proposed which purport to address elements lacking in the primary references GR ‘510, KR ‘994, and Coquelet. The obviousness rejections can be grouped as follows (1) preferred free radical agonists (claims 5-12); (2) pH of 5.5 to 6.0 (claim 4); (3) concentration of 2 to 50 mg/L (claim 16). For reasons explained below, the original claims 4, 5, and 16 are non-obvious in view of the cited references.

#### **Preferred Free Radical Agonists (claims 5-12)**

The Office Action proposes that it would have been *prima facie* obvious to substitute the sodium metabisulfite of GR ‘510, KR ‘994 and Coquelet with one of the specifically listed free radical antagonists categories listed in claim 5, citing Handbook ’79 and Cole as support for these substitutions:

Claims 5, 6, 8, 10, and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over GR ‘510 as applied to claims 1-3, 9, 11, 13-15, and 19, further in view of Handbook ’79 and Cole.

Claims 5, 6, 8, 10, 12, and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over KR ‘994 as evidenced by Hayatsu and

as applied to claims 1, 3, 9-11, 14, 15, 17 and 18, further in view of Handbook '79 and Cole.

Claims 5, 6, and 8-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Coquelet as applied to claims 1, 3, 13, 14 and 16, further in view of Handbook '79 and Cole.

Claim 5 depends from claim 1 and thus requires a *stable* formulation with three specific kinds of free radical antagonists, as follows:

1. A *stable*, liquid formulation consisting essentially of acetaminophen dispersed in an aqueous medium containing a buffering agent and at least one member of the group consisting of *a free radical scavenger and a radical antagonist*.
5. The formulation of claim 1 containing a free radical antagonist selected from the group consisting of *ascorbic acid, ascorbic acid derivatives, organic compounds having at least one thiol, and alkyl polyhydroxylated and cycloalkyl polyhydroxylated compounds*.

As discussed above, neither GR '510, KR '994 nor Coquelet achieved stability. GR '510 utilized an aqueous media that included nearly 50% glycerol formal, and Dr. Craig's testing showed this composition exhibited several secondary peaks by HPLC. The KR '994 and Coquelet formulations similarly observed secondary peaks. Neither of these references disclose removal of oxygen dissolved in the carrier, which the '222 patent describes as being a condition upon which stability depends. '222 patent, col. 2, ll. 31-35. Each of GR '510, KR '994 and Coquelet disclose an amount of sodium metabisulfite. The Office Action proposes substitution of sodium metabisulfite with ascorbic acid citing Handbook '79 and Cole.

Initially, the proposed modification of KR '994 and Coquelet with Handbook '79 and Cole is improper and these combinations cannot result in a prima facie case of obviousness. The Office Action relies on the sodium metabisulfite of KR '994 as the buffering agent, stating "sodium metabisulfite can also serve as a buffer." OA at 17. While the Office Action suggests

that it is *prima facie* obvious to replace the antioxidant sodium metabisulfite with ascorbic acid, the Office Action fails to show how ascorbic acid can serve as a buffering agent. Where the proposed modification results in a product that does not meet the claimed limitations, a *prima facie* case of obviousness has not been established.

Second, Coquelet discloses an ophthalmic composition. The examiner cites Handbook '79 and Cole for teachings on why systemic administration of sodium metabisulfite may be discouraged. However, these references do not discuss whether there is any reason to replace sodium metabisulfite in an ophthalmic composition. Each of the reasons provided by Handbook '79 and Cole appear inapplicable to ophthalmic compositions. Further, combining references that are not in the same field of endeavor and which do not relate to the same problem solved is improper.

Regarding each of the proposed modifications of GR '510, KR '994 and Coquelet, while the Office Action states that sodium metabisulfite may have issues, there is no reason or motivation cited to replace sodium metabisulfite with one of the three categories of free radical agonists listed in claim 5. The Office Action merely points to a list of known antioxidants and proposes swapping sodium metabisulfite with ascorbic acid. The list of antioxidants, however, is extensive:

Ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), hydroquinone, lecithin, nordihydroguaiaretic acid, phenyl alpha-naphthylamine, propyl gallate (and octyl and dodecyl gallates), alpha-tocopherol, acetone sodium bisulfite, ascorbic acid, cysteine hydrochloride, isoascorbic acid, sodium bisulfite, sodium formaldehyde, sulfoxylate, sodium metabisulfite, sodium sulfite, thioglycerol, thioglycolic acid, and thiosorbitol.

Handbook '79 at 96-97. Moreover, the Office Action states that once selected, the ascorbic acid will inherently serve as a free radical agonist. However, there is no motivation to pick from the list of Handbook '97 one of the specifically listed free radical antagonists in order

to meet the claimed invention. For these reasons, the combinations of GR '510, KR '994 and Coquelet with Handbook '79 and Cole fails to raise a *prima face* case of obviousness with respect to claims 5-12.

#### Unexpected Results

Comparative data has been presented showing that OFIRMEV has an unexpectedly improved stability relative to GR '510, KR '994, and Coquelet. Craig, ¶¶ 33-52. Specifically, Dr. Craig reproduced and tested GR '510, KR '994 and Coquelet, and demonstrated that these compositions exhibited secondary peaks upon testing with HPLC, and would not have had a pharmaceutically acceptable shelf life. In addition, the lack of secondary peaks has been shown for several compositions prepared in accordance with claim 5. For example, Dr. Craig tested four acetaminophen compositions falling within the scope of claim 5 and showed that these compositions confer stability under the '222 patent. Craig, ¶¶ 47. The inventor, Dr. Dietlin, has submitted additional data showing compositions within the scope of claim 5 that show further stability. Dietlin, ¶¶ 1-20. Dr. Craig has reviewed these data and confirms the testing is additional evidence that several compositions within the scope of claim 5 meet the claimed stability limitation. Craig, ¶¶. 48-50. Accordingly, there is no dispute that the unexpected properties established for OFIRMEV also apply to other compositions meeting the limitations of claim 5. Based on these data the showing of unexpected results is reasonably commensurate in scope with at least claim 5. *In re Kao*, 637 F.3d 1057, 1068 (Fed. Cir. 2011) ("If an applicant demonstrates that an embodiment has an unexpected result and provides an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, this will generally establish that the evidence is commensurate with scope of the claims.")

In addition, the showing of unexpected results further supports dependent claims 6-10, which set forth more specific species included within claim 5.

Secondary Considerations – Commercial Success and Long Felt Need

The '222 patent claims the first approved injectable formulation of acetaminophen (*i.e.*, paracetamol or N-acetyl-p-aminophenol) in the United States, OFIRMEV® injection. Buvanendran, ¶ 47. The European equivalent is Perfalgan®, launched in 2002. *Id.* According to its prescribing information:

OFIRMEV injection is a sterile, clear, colorless, non pyrogenic, isotonic formulation of acetaminophen intended for intravenous infusion. It has a pH of approximately 5.5 and an osmolality of approximately 290 mOsm/kg. Each 100 mL contains 1000 mg acetaminophen, USP, 3850 mg mannitol, USP, 25 mg cysteine hydrochloride, monohydrate, USP, 10.4 mg dibasic sodium phosphate, USP. pH is adjusted with hydrochloric acid and/or sodium hydroxide.

Exhibit A (OFIRMEV prescribing information).

The '222 patent addressed a long felt yet unmet need in the marketplace for a “stable, liquid formulation consisting essentially of acetaminophen dispersed in an aqueous medium” suitable for injection. The closest injectable composition on the marketplace was sold in Europe as a prodrug of acetaminophen under the trade name pro-Dafalgan®. *Id.*, ¶ 50. The instability of pro-Dafalgan in water was widely recognized—it was sold as a powder that had to be reconstituted. *Id.* Reconstitution entailed risks for the healthcare provider and precluded use of pro-Dafalgan in time sensitive, emergency circumstances. *Id.*, ¶ 50-51. Finally, pro-Dafalgan users experienced “high incidence of pain at injection site.” *Id.*, ¶51.

The '222 patent's commercial product OFIRMEV® and its European equivalent Perfalgan® are commercially successful, and that success derives from these products being the first stable, liquid injectable form of acetaminophen. By second quarter 2012, Ofirmev® accounted for 66 percent of U.S. sales of non-opioid analgesics suitable for IV administration. Bell, ¶ 9. Since its launch in 2002, Perfalgan (identical to OFIRMEV) became the top grossing non-opioid analgesic suitable for IV administration in France, Germany, Spain, Italy, and the United Kingdom. *Id.*, ¶10. The '222 patent product achieved these sales numbers even though they have a wholesale acquisition cost (WAC) that is approximately 170 times that of

acetaminophen tablets and 40 times that of acetaminophen suppositories. *Id.*, ¶ 11. Finally, the commercial success of OFIRMEV is not due to marketing or the merits of acetaminophen in general, *Id.*, ¶ 12.

The '222 patent teaches that the problem with liquid injectable formulations of acetaminophen at the time of the invention was lack of stability. The key breakthrough of the '222 patent invention the discovery by the inventors that the degradation of acetaminophen involves first an oxidative process followed by hydrolysis. Elder, ¶44; '222 patent, col. 10, ll. 41-43. To this end, the '222 patent requires a *stable*, liquid composition. Stability, according to the '222 patent, requires the absence of secondary peaks using an HPLC analysis. Further, the specification makes clear that stability requires, in addition to careful choice of the carrier, "careful adjustment of pH, removal of oxygen dissolved in the carrier and addition of a free radical antagonist or a free radical scavenger." '222 patent, col. 2, ll. 31-35. Each of the cited references lacks one or more of the claimed features, results in an unstable product, and fails to render the claimed invention obvious.

Injectable acetaminophen compositions prepared in accordance with the processes described in the '222 patent exhibit the unexpected stability. The grounds of rejection are based on three primary references: (1) GR870101510B ("GR '510"), (2) KR 1993-0011994 ("KR '994"), and (3) U.S. Patent No. 5,270,050 ("Coquelet"). Each of the prior are references cited lacks the claimed stability limitation as shown by the presence of secondary peaks in an HPLC analysis. Craig, ¶¶ 32-41, 52. The lack of stability in these products is not surprising since the prior art references fail to follow the teachings of the '222 patent with respect to obtaining a stable, liquid acetaminophen composition. Further, these references further lack the improved characteristics obtained with the compositions of claim 5, which require specific free radical antagonist or scavengers that allow for reduced injection site pain and thus reduce the need for local anesthetic in the composition (*i.e.*, a composition consisting essentially of acetaminophen in an aqueous media). The Office Action fails to set forth persuasive reasoning why a person having ordinary skill in the art would have replaced sodium metabisulfite with an antioxidant.

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Further, unexpected results, comparative testing, and secondary factors weigh heavily toward a finding of non-obviousness.

For each of the foregoing reasons, claims 5-12 are nonobvious in view of GR '510, KR '994 and Coquelet in view of Handbook '79 and Cole.

***New Claims***

The new claims further distinguish the cited prior art for reasons beyond the stability and other limitations addressed above. For example, the new claims requiring a pH below 6 further distinguish over the higher pH levels described in KR '994 and Coquelet, while the acetaminophen concentration range of 5 to 20 mg/mL further distinguishes over the higher concentrations of GR '510. For at least these reasons, the new claims are allowable over the prior art for reasons in addition to those discussed above with respect to claim 1.

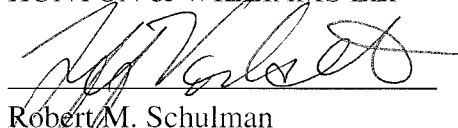
***Conclusion***

For the foregoing reasons, Patent Owner respectfully requests confirmation of original claims 1-6, 8-13, and 16-19 and newly added claims 29-43 of the '222 patent.

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By:

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